

X-linked Hyper-IgM Syndrome Associated With a Rapid Course of Multifocal Leukoencephalopathy

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Objective: To report an exceptional association between X-linked hyper-IgM syndrome and progressive multifocal leukoencephalopathy.

Design: Clinical, immunological, and histological analysis.

Patient: A 19-year-old male patient with X-linked hyper-IgM syndrome developed typical signs and symptoms of progressive multifocal leukoencephalopathy.

Results: The serum level of IgA was decreased; the serum level of IgM was slightly increased; and the serum level of IgG was normal as a result of monthly infusions

of immunoglobulin. The expression of CD40 ligand on T cells was markedly reduced in the patient. Magnetic resonance imaging indicated confluent lesions involving the majority of the right hemisphere with a mass effect. The patient died after 6 weeks despite combined antiviral treatment.

Conclusion: Progressive multifocal leukoencephalopathy may follow a rapid course in patients with X-linked hyper-IgM syndrome because of global defects of cellular and B cell responses.

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X-LINKED HYPER-IGM SYNDROME (X-HIGM) is a rare primary immunodeficiency disorder caused by a mutation in the gene encoding for CD40 ligand (CD40L) expressed on the surface of activated T cells.^{1,2} This molecule is necessary for T cells to induce isotype switching in B cells by binding to CD40. Because of the class switch recombination defect, patients with HIGM have decreased serum levels of IgG, IgA, and IgE, and elevated or normal levels of serum IgM.³ Signals generated by CD40L are also important in priming T cells and inducing IL-12 production by macrophages and dendritic cells.⁴ Thus, in addition to the defective production of antibodies, cellular immune responses that are critical for protection against intracellular pathogens are also impaired.

Progressive multifocal leukoencephalopathy (PML) is a rare demyelinating disease of the central nervous system. The disease is caused by opportunistic infection by the JC virus (JCV).⁵ The primary infection is common and usually remains asymptomatic. The virus resides in the kidney in a latent form and can be reactivated when the immune system becomes

compromised. B cells may transmit the virus to oligodendrocytes in the brain. Lysis of oligodendrocytes results in multiple and progressive central nervous system symptoms.

Progressive multifocal leukoencephalopathy affecting patients with congenital immunodeficiencies is exceptional.^{6,7} Herein, we report a unique association between X-HIGM and PML, which resulted in an unusually rapid progression that led to death within 6 weeks despite antiviral treatment.

CASE REPORT

A 19-year-old right-handed male patient was admitted to our neurology department because of progressive left faciobrachial paresis. He had been treated for X-HIGM since the age of 3 years. His brother died of pneumonia at 9 years of age after several recurrent episodes of aphthous stomatitis, upper and lower respiratory tract infections, purulent otitis media, mastoiditis, and bacterial pneumonia. Sequence analysis of the *CD40L* gene in the patient revealed a hemizygous C→A transversion at nucleotide position 216 in

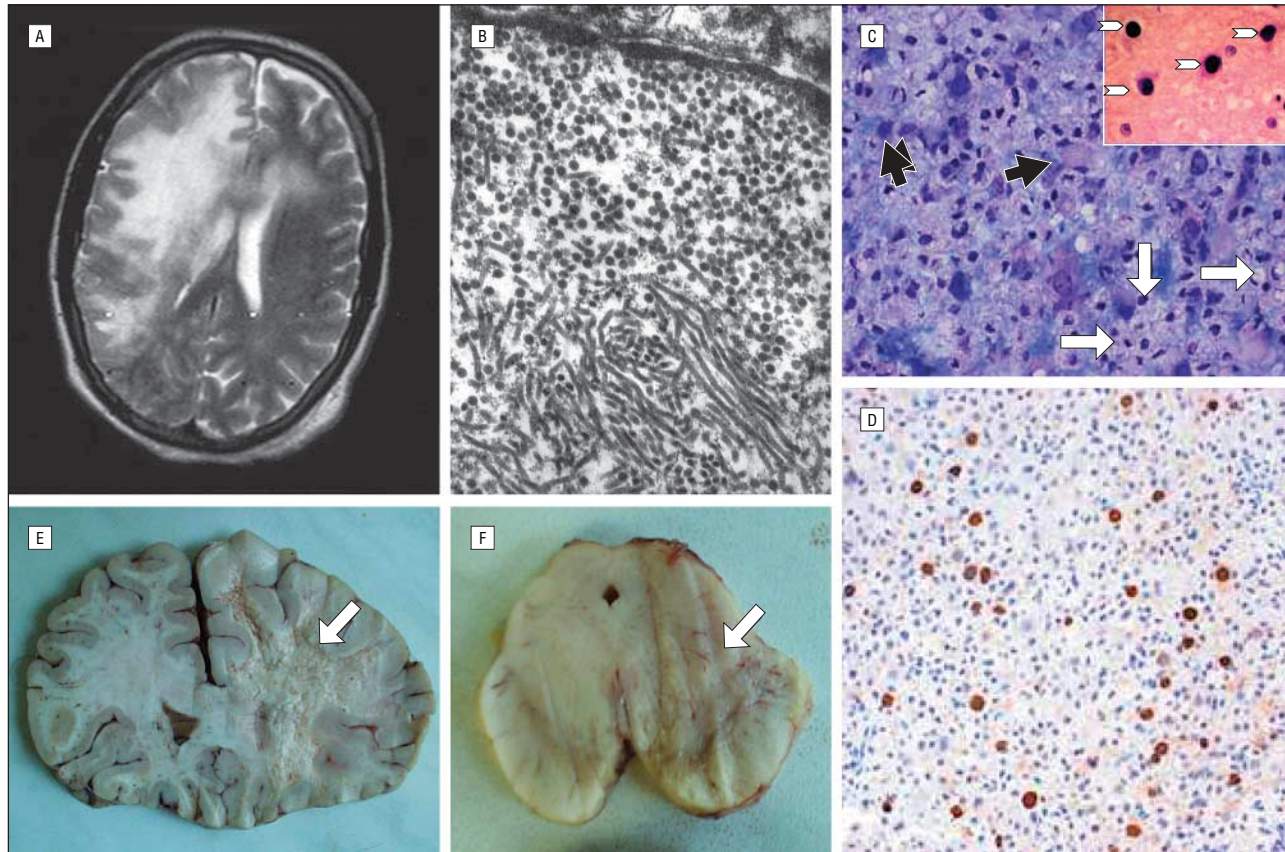


Figure. Magnetic resonance imaging and pathology of the brain in a patient with rapidly progressive multifocal leukoencephalopathy. A, Magnetic resonance imaging of the brain shows large confluent lesions in the right hemisphere with a slight compression of the third ventricle on T2-weighted images. B, Electron microscopy of brain biopsy specimen shows nuclear inclusions corresponding to JC virus particles in oligodendrocytes (original magnification $\times 40\,000$). Histology of a brain biopsy sample shows giant astrocytes (C, black arrows), lipid-laden macrophages with vacuoles (C, white arrows) (original magnification $\times 200$), and scattered oligodendrocytes loaded with nuclear inclusions (C, insert, arrowheads) (original magnification $\times 400$) corresponding to Polyomavirus particles positively stained by a polyclonal cross-reactive antibody against simian virus 40 (SV40) polyoma subgroup (D) (original magnification $\times 200$). E and F, Numerous small and large confluent foci of the hemispheric white matter and the mesencephalon were detected (arrows). Some of the foci are partly cavitated.

exon 2 and heterozygosity for this mutation in the genomic DNA from his mother. This mutation resulted in stop codon at amino acid 72 (p.C72X). Expression of CD40L was tested by flow cytometry as previously described.⁸ Heparinized whole blood samples were activated with 10 ng of phorbol myristate acetate per milliliter of blood (Sigma-Aldrich Corp, St Louis, Mo) and 250 ng of ionomycin per milliliter of blood (Calbiochem, San Diego, Calif) for 4 hours at 37°C in an atmosphere containing 5% carbon dioxide. Anti-CD69 staining was performed as a positive control to T cell activation.⁸ The expression of CD40L on CD4+ CD69+ T cells of the patient was 4% in contrast to 100% of control cells. The patient was treated with regular monthly intravenous immunoglobulin infusions and occasionally with recombinant human granulocyte colony-stimulating factor because of recurrent neutropenia. He developed severe opportunistic infections, including *Cryptococcus laurentii* meningitis and esophageal candidiasis.⁹ One year before his admission, a hepatitis C virus infection was diagnosed, but no treatment had been initiated because of his neutropenia.

On admission, the patient complained of dizziness and an unsteady gait, followed by weakness of his left extremities and apathy after 4 days. Neurologic examination revealed left central facial and hypoglossus nerve

palsy, visual neglect, left-sided hemiparesis with increased deep tendon reflexes, the Babinski sign, and spasticity. Decreased proprioceptive sensation was found on the left side of the body. His movements, speech, and attention were slowed, but memory and body perception were maintained; neither aphasia nor apraxia was detected. Electroencephalography showed a nonspecific diffuse slowing of background activity above the right frontotemporal regions. Cerebrospinal fluid examination revealed normal protein levels (0.25 g/L) and glucose content without cells. No intrathecal immunoglobulin synthesis or damage of blood-brain barrier were found (IgG index, 0.7) (no oligoclonal bands were detected by isoelectric focusing). Cultures were negative for bacteria and fungi. Antiviral antibodies for cytomegalovirus, varicella-zoster virus, herpes simplex virus 1, and herpes simplex virus 2 were not found; herpes simplex virus type 1 DNA could not be detected by polymerase chain reaction in the cerebrospinal fluid. Serology tests were negative for the human immunodeficiency virus (HIV). Immunoglobulin levels in the serum were measured twice. IgG levels were normal (6.9 g/L; normal range, 6-16 g/L), IgM levels were slightly increased (2.18 g/L; normal range, 0.5-2.0 g/L), and IgA levels were reduced 4 days after the patient's first symptoms (<0.2 g/L; normal range, 0.8-

4.0 g/L); similar results were obtained 1 month later (IgG, 8.5 g/L; IgM, 3.16 g/L; IgA, 0.1 g/L). Serial cranial magnetic resonance imaging showed 2 large lesions with a high signal on T2-weighted images and a low signal on T1-weighted images in the white matter of the right frontal and temporal lobes. The lesions progressively extended into the right side of the brainstem and into the left hemisphere through the corpus callosum (Figure, A). None of the lesions showed contrast enhancement, and the ipsilateral third ventricle was slightly compressed.

Brain biopsy revealed hypertrophic giant astrocytes, lipid-laden macrophages with vacuoles, and scattered oligodendrocytes loaded with nuclear inclusions (Figure, B and C). The oligodendrocytic inclusions were positively stained by a cross-reactive, polyclonal antibody against simian virus 40 (SV40) polyoma subgroup (dilution, 1:200)¹⁰ (Figure, D). Based on the clinical, histological, and immunohistochemistry findings, PML was diagnosed, and thus polymerase chain reaction for JCV in the cerebrospinal fluid or in situ hybridization was not performed. The patient was treated with a combination of interferon alpha (3 million IU, subcutaneously, 3 times a week) and ribavirin (1200 mg daily), but he died without improvement after 6 weeks.

Autopsy was performed and the formalin-fixed brain was cut 4 weeks after death. Coronal brain slices confirmed asymmetrically confluent areas of abnormal parenchyma with cavitation of the white matter in the brain and the brainstem (Figure, E and F).

COMMENT

The remarkably rapid progression of PML and the unusually large lesions involving the major part of the right hemisphere suggested an unlimited propagation of JCV. While absence of contrast enhancement was typical and helpful in differentiation of PML from central nervous system lymphoma, the involvement of the frontal lobe and the mass effect were somewhat atypical.

Progressive multifocal leukoencephalopathy has been increasingly detected in patients with AIDS and other secondary immunodeficiency conditions.¹¹⁻¹³ However, the disease is exceptional in primary immunodeficiencies, and only a single case of PML associated with X-HIGM has been reported.⁷ The central importance of T cells in containing the replication of viruses is well established.¹⁴⁻¹⁶ Thus, a reduced number of CD4+ T cells and impaired PML-specific CD8+ T cell responses may justify the high frequency of PML in acquired immunodeficiencies.¹⁷⁻¹⁹ In contrast, the number of T cells is retained in X-HIGM, which may explain the rarity of PML. However, impaired cellular immune responses should play a central role in the evolution of PML in X-HIGM as well, because serum levels of IgG were normal and serum levels of IgM were slightly increased while PML rapidly progressed in our patient. The markedly reduced CD40L on T cells certainly interferes with T cell activation because of a deficient costimulation in X-HIGM. The altered costimulation may result in decreased priming of T cells and production of interferon- γ as well as impaired functions and IL-12 production of macrophages and den-

dritic cells.²⁰ Moreover, CD8+ T cell responses, which are crucial in the early control of PML, will also be deficient.¹⁸⁻²⁰ Thus, once reactivation of PML occurs, the disease may rapidly progress in X-HIGM because of the severely compromised immune responses affecting both T cell- and B cell-mediated immunity. Reactivation of JCV by HIV through Tat, one of the HIV-encoded transregulatory proteins, has been implicated.²¹ Our patient was not infected with HIV, but hepatitis C virus infection was detected 1 year before PML developed. Whether the hepatitis C virus could play a role in reactivation of JCV remains obscure.

Efficient therapies have not been established for patients with PML. Antiviral agents, highly active antiretroviral treatment in AIDS, and immunotherapies like interferon alpha may be beneficial in acquired and iatrogenic immunodeficiency.²² In our case, combined interferon alpha and ribavirin treatment was ineffective, and the disease progressed rapidly to death.

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